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Assessment of Painful Episode Frequency in Sickle-Cell Disease

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Frequency of painful episodes in sickle-cell disease is considered to be related to clinical severity and possibly to other aspects of the disease. Measurements of frequency often include only hospital-related or more severe, longer-lasting episodes. Since painful episodes, however, may regularly occur in nonhospital settings or be shorter-lasting with possible different pathologic effects, we measured all painful episodes in 10 adults with sickle-cell disease for 1.0–3.8 years, using a daily questionnaire. The results were related to other indices of disease severity and to possible precipitating factors, such as cold weather and menses. Sixty-one percent (on average) of the total number of episodes (243) were nonhospital-related, and 33% (on average) were shorter-lasting. Episode frequencies, whether determined as total, hospital-related, nonhospital-related, or shorter-lasting, were not related to each other or to other indicators of disease severity. The highest incidence of episode frequency occurred in the winter. The association of episodes with menses was moderately close in individual patients. The findings suggest that nonhospital-related painful episodes and shorter-lasting episodes may contribute significantly to episode frequency. Measurement of frequency of all painful episodes would require consideration when evaluating episode frequency and its relationship to disease severity, to possible precipitating factors of episodes, and to treatment of the disease, and for study of the natural course of the disease. Am. J. Hematol. 54:183–188, 1997

Key words: painful episode; sickle-cell disease; frequency

INTRODUCTION

Painful episodes in sickle-cell disease are a major complication of the disease and occur with various degrees of frequency. Since frequency of episodes may be an indicator of clinical severity and could be an important measure for evaluation, prognosis, treatment [1–3], and follow-up of the natural course of the disease, detailed recording of episode frequency could be important. Evaluation of frequency is generally determined by measurement of the number of hospital/emergency room admissions or by measurement of frequency of the more severe, longer-lasting episodes, and this evaluation ignores nonhospital-related or shorter-lasting episodes. Since nonhospital-related episodes may occur regularly [4–7] and shorter-lasting episodes may have different pathologic changes [8–11], evaluation of the frequency of nonhospital and of shorter-lasting episodes [12] may allow for a more accurate evaluation of the relationship between episode frequency, clinical and disease severity, and organ damage, as well as providing information on the natural course of the disease.

Detailed measurement of episode frequency over extended periods of time may also be important, since frequency may fluctuate significantly due to seasonal

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weather changes [13], clustering of episodes [14], or random variation. Measurements of frequency of all episodes over prolonged periods could clarify the significance of factors, such as cold weather, or other factors in the precipitation of painful episodes.

In the present study, we have 1) determined the frequency of nonhospital-treated painful episodes as compared to the frequency of hospital-related episodes using a daily questionnaire over a prolonged period of time; 2) compared the frequency of different types of episodes to other measures of vasocclusive or hematologic severity and to each other; and 3) examined the relationship of episode frequency to possible precipitating factors such as seasonal weather changes and menses.

PATIENTS AND METHODS

Fifteen adults, age 21 years and older, with sickle-cell disease as confirmed by clinical and hematologic criteria, were entered into the study. Patients who were selected for study generally had long-term association with the Hematology Clinic at Mount Sinai Hospital and had been reliable and compliant in previous studies in our program. Several patients had been followed throughout the study. Five of the original 15 patients were removed due to unsatisfactory compliance, i.e., due to inadequate or inaccurate record keeping, failure to keep appointments, or moving to other areas. The patients with diaries were studied from 1.0–3.8 years.

The patients had relatively few previous complications from disease and were asymptomatic from painful episodes and from these complications during the period of study. No medications other than analgesics (generally acetaminophen) or antibiotics during acute infections were given during the study. Previous Pneumovax vaccination had been given to 2 patients. No transfusions were given while on the study or for at least 1 year prior to starting the study.

Questionnaires for daily assessment of pain were used to determine the frequency of painful episodes. The questionnaires were devised so that they could be readily answered and would be suitable and practical for long-term use by out group of patients [12]. Clarification and explanation of the study and of the questions in the questionnaire were done prior to start of the study and generally at 4–8-week follow-up visits at which time diaries were collected.

The questionnaires contained five primary questions requiring yes/no answers: 1) Did you take pain medicine at home today for ''sickle pain?'' 2) did you go to the emergency room today for ''sickle pain?'' 3) Were you admitted to the hospital today for a ''pain crisis?'' 4a) Do you have a cold today? b) Do you have the ''flu'' today? c) Do you have a temperature today? and 5) For women: do you have your period today? During the first 7 months of the study, the questionnaire consisted of the first three questions.

During preliminary studies, the above yes/no questionnaire and a visual analogue test for pain evaluation [16] were used. The latter test was discontinued because of unsatisfactory compliance. Patients did not always fully understand the method of designating pain severity, and the resulting confusion gave rise to unclear and inconsistent reports and failure to do timely recording. In 3 patients who did reliably follow both methods for approximately 3 months, both methods showed similar recordings.

Compliance to satisfactory diary recording was supported in several ways. Supportive interviews at 4–8-week intervals were carried out during clinic visits, and the importance of careful and regular recording in the diary was emphasized. Compliance and reliability of the diary recording were corroborated by direct comparison of hospital/emergency room records and the patients' daily records. Previous findings have shown the validity of diary use for pain measurements [16]. Emergency room visits were not recorded as separate episodes if they were associated with a hospital admission. The questionnaires in general were maintained consecutively during the period of study. The patients were not paid to participate in the study.

Sickle pain was considered to occur if the patient required analgesics for pain which was similar to the pain(s) which occurred during typical painful crises. This approach allowed for a definable indicator of pain which addresses some of the difficulties with pain evaluation which arise from its subjective nature, and from differences in pain threshold among individuals. The approach thus followed earlier study designs in which a ''patient-oriented . . . working definition of an episode of pain'' was used [1,3,12]. A painful episode was considered to occur if analgesics were required during a 1-day period or longer, if the episode was separated by at least 2 days from another diary-recorded episode, if the patient visited an emergency room for treatment of sickle disease pain, or if the patient was admitted to the hospital for a painful crisis.

Shorter-lasting episodes, i.e., episodes which required analgesic up to 48 hr, were arbitrarily divided into those which required analgesic up to 24 hr (24-hr shorter-lasting), and those which required analgesic up to 48 hr (48-hr shorter-lasting), since the precise length and significance of these limited ischemic episodes are not known [8–11]. The 24-hr episodes were not included in the 48-hr episodes.

Seasons were defined as winter (December, January, and February), spring (March, April, and May), summer (June, July, and August), and fall (September, October, and November). Eight of the 10 patients were evaluated for seasonal incidence of painful episodes. Two patients

TABLE I. Clinical and Laboratory Data on Patients With Sickle-Cell Disease

Patient	Dx	Age	Gender	Clinical findings[a]	Hb (g/dl)	Fetal Hb (%)	Retic × 10/l	RDW units	WBC × 10/l	Ca^{2+} vesicles (%)[b]
1	SS	29	F		9.5	13.9	25.2	18	15,800	43
2	SS	40	F		8.1	1.4	24.1	25	13,200	
3	SS	33	F	Severe leg ulcers	6.8	12.4	38.3	24	17,500	33
4	SS	26	F		7.3	3.9	22.1	24	8,600	
5	SS	37	F		7.2	3.9	44.6	23	13,800	36
6	SC	21	M		12.7	0.6	25.4	16	9,400	
7	SS	25	F		6.4	3.1	35.0	21	12,200	
8	SS	47	F		7.1	0.7	26.0	21	13,100	23
9	SS	67	F	Severe leg ulcers Severe osteonecrosis	6.9	5.7	46.8	24	12,900	15
10	SC	23	F		11.3	0	18.1	17	9,800	

[a]Refers to presence of leg ulcers or osteonecrosis.
[b]Percentage of red blood cells with intracellular Ca^{2+}-containing vesicles (normal, 0–2%).

who were followed for only 1 year were not evaluated for seasonal incidence because a gap in their dairies was noted which did not allow for satisfactory analysis.

The occurrence and length of menses were obtained from the diaries. The menses were considered to overlap with the painful episodes if complete overlap occurred or if an episode occurred within 48 hr prior to or after a menstrual period. The relative risk of sickle pain itself occurring during menses as compared to the risk of sickle pain itself occurring during nonmenstrual periods was obtained by dividing the probability of sickle pain occurring during menses by the probability of sickle pain occurring during nonmenstrual periods. The probability of sickle pain itself occurring during menses was obtained by dividing the number of days with sickle pain which occurred during menses divided by the number of menstruating days plus 4; the probability of sickle pain itself occurring during nonmentual periods was the number of days with sickle pain which occurred during nonmenstruating days divided by the number of nonmenstruating days minus 4 days. Two of the patients were not included in the evaluation. One patient was postmenopausal, and the other patient had no painful episodes. Seven of the 9 patients had been pregnant. Four had one pregnancy and 3 had two pregnancies. Pregnancies in the latter group were separated by 2–8 years.

Hemoglobin levels, reticulocyte counts, relative distribution width (RDW) of red blood cells, and platelet counts were determined by standard methods. The values were the means of at least four determinations. Hemoglobin F was obtained by hemoglobin electropheresis and alkalai denaturation. Fetal hemoglobin levels were determined within 2 years prior to start of the study. The patients were age 21 years or older, after which fetal hemoglobin levels are relatively stable. Intracellular Ca^{2+}-containing vesicles were determined by microscopy after staining the cells with the fluorescent probe, chlortetracycline, as previously described [17].

Statistical evaluation was obtained by the Spearman rank correlation coefficient to test for association between various numbers of episodes and various clinical variables. The signed rank test was used to compare the average number of episodes for each season to the other seasons and to compare the relative risk of pain during menses to 1.0 (the log relative risk is compared to 0). Nonparametric tests were appropriate due to the small sample size and nonnormal appearance of distributions [18].

RESULTS

The clinical and laboratory findings of the patients are shown in Table I. The table also includes the percentage of red cells with intracellular Ca^{2+}-containing vesicles, which are related to clinical severity in sickle-cell disease (SCD) [19]. Table II includes general information about frequency of episodes. The average total number of painful episodes per year was 14 (range, 0–35). The total number of painful episodes for all patients during the period of study was 243, of which 63% (average) (range, 0–100%) were nonhospital-related. The percentage of total episodes which were shorter-lasting episodes was 33% (on average). Twenty percent (average) of the total episodes were 24-hr, shorter-lasting episodes (range, 4–24%), while the percentage of total episodes which were 48 hr, shorter-lasting episodes was 13% (on average; range, 0–25%). The average number of years during which the questionnaires were kept was 1.9 years (range, 1.0–3.8 years), and the total number of person years during which the diaries were kept was 18.5 years. Rates of individual patient pain were variable over the years of study. The frequencies were unpredictable except in patients who were pain-free during the period of study.

The relationship between outpatient and inpatient episode frequencies was not significant ($r = 0.35$, $P = 0.32$). The frequency of total episodes, hospital-treated, or outpatient episodes was not related to fetal Hb levels,

TABLE II. Painful Episode Frequency in Patients With Sickle-Cell Disease*

Patient	Dx	Length of diary (years)	Total PE pa	Outpt PE % total PE	Total SPE (24-hr) % total PE	Total SPE (48-hr) % total PE
1	SS	2.3	18	72	22	22
2	SS	1.4	9	77	42	25
3	SS	2.4	34	59	6	15
4	SS	3.8	0	NA	NA	NA
5	SS	1.1	28	71	4	7
6	SC	1.6	6	67	33	0
7	SS	1.6	8	0	8	8
8	SS	1.0	35	100	29	20
9	SS	1.4	0	NA	NA	NA
10	SC	1.9	7	43	14	7

*PE, painful episodes; Outpt, outpatient; NA, not applicable; pa, per year; SPE, short-lasting painful episodes.

blood Hb levels, RDW, or to the level of reticulocyte counts. *r* values for relationships were between −0.11–0.50, with *P* values between 0.39–0.78. The power to detect these magnitudes of correlation with our sample size was between 5–33%.

The total number of episodes occurred more frequently in winter (6.55 episodes, on average) as compared to the rest of the year (spring, 4.24; summer, 4.46; and fall, 4.80). Results of the signed rank tests comparing winter vs. fall, winter vs. summer, winter vs. spring, fall vs. summer, all vs. spring, and summer vs. spring were 0.2500, 0.0078, 0.0547, 0.6406, 0.4509, and 1.000, respectively. Using a Bonferroni correction for multiple comparisons, an alpha-level of 0.0083 was required for each of the six comparisons to ensure an overall alpha-level of 0.05 (0.05/6 = 0.0083). By these criteria, a statistically significant difference was observed between winter and summer ($P = 0.0078$) for seasonal pain. Three patients had the highest incidence of painful episodes in winter, while the highest incidence of episodes in the remaining patients for other seasons was distributed evenly among the other patients.

The relationship between menses and painful episodes is shown in Table III. Forty-two percent (average; range, 25–71%) of painful episodes were associated with menses, and 69% (average; range, 19–100%) of menses were associated with painful episodes. The relative risk of sickle pain itself occurring during menses as compared to nonmenstrual time was 1.49 (average; range, 0.74–2.43). The *P* value for the nonparametric test of relative risk as compared to 1.0 was 0.16. Menses data were not reported in 2 patients, since one patient was postmenopausal and the other patient had had no painful episodes during the period of the study. No patients became pregnant or were known to be on hormonally-based birth control. There did not appear to be a difference between out- and inpatient painful episodes with menses.

DISCUSSION

The findings demonstrate that painful episodes may occur frequently in nonhospital settings in patients with sickle-cell disease (61%, on average), and that the frequency of episodes in nonhospital settings does not show a significant relationship to the frequency of hospital-treated episodes. As such, assessment of clinical severity using hospital-related episodes alone for evaluation of episode frequency can differ markedly from assessments in which both hospital and nonhospital, i.e., total painful episodes, are included. This would affect evaluation of clinical or disease severity. Underestimation of frequency of painful episodes is supported by the observation that >40% of patients with SCD did not seek pain relief during a 5-year follow-up period [1]. The findings would further suggest that evaluation of all painful episodes is important when evaluating the response of patients to treatment of painful episodes and during studies on the natural course of the disease.

Selection bias, including sample size and gender disproportion, were important considerations in our evaluation of the results. The population which was studied was highly selected, because a very compliant and responsible group of patients was required. Although the number of patients studied was relatively small and the patients were predominantly women, the primary aim of the study and the nature of the data base permitted the extraction of relevant conclusions.

The primary aim was to determine the frequency of nonhospital-treated painful episodes and to determine their relationship to hospital-related or total episode frequency. As such, measurement of episode frequency was the important determination. Frequency data consisted of a long and detailed study of each patient (1.0–3.8 years), giving a total of 18.5 person years of data. The total number of painful episodes was 243 for all patients during the period of study, of which 61% were nonhospital-treated. This data base was sufficient to address our aims

TABLE III. Menstrual Data on Patients With Sickle-Cell Disease*

Patient	Total PE	Total menses	PE associated with menses	% of total PE associated with menses	% of total menses associated with PE	Relative risk of sickle pain during menses[b]
1[a]	39	20	16	41	80	2.41
2	12	16	3	25	19	1.06
3	76	27	27	36	100	0.99
5	31	12	12	39	100	1.57
7	12	14	5	42	36	1.24
8	35	14	14	40	100	2.43
10	14	20	10	71	50	0.74

*PE, painful episodes.
[a]Numbers correspond to Table I.
[b]Relative risk of sickle pain during menses as compared to nonmenstrual time.

and yield conclusions which met statistical criteria for significance.

Indicators of clinical and disease severity, such as fetal Hb levels, blood Hb levels, RDW, and reticulocyte counts, were evaluated for their possible association with episode frequency. Statistical analyses did not show significant relationships. This conclusion, however, was affected by sample size, which provided sufficient power (80%) to detect only correlations of 0.77 or more. The results may only confidently be applied to women, since 9 of the 10 patients were women. The results in this limited study, however, do suggest that episode frequency may be an independent indicator of disease severity. The findings support a previous observation that painful episodes are independent risk factors for the development of painful episodes [20], and an earlier concept that painful episodes are related to multiple gene defects [21].

The shorter-lasting episodes, which appear to be associated with limited tissue ischemia and may not be associated with permanent tissue damage [8–11], also occur frequently. Thirty-three percent (on average) of total episodes were shorter-lasting. Twenty percent of total episodes were 24-hr episodes, and 13% were 48-hr episodes. These findings could be important, since the frequency of these episodes could effect evaluation of clinical or disease severity, and might also better define the relationship of painful episodes to organ damage. These episodes may further contribute to the patient's perception of his disease, and to his concepts of the effects of therapy for the episodes, as well as to a better understanding of the natural course of the disease.

Precipitation of painful episodes in sickle-cell disease has been related to numerous factors, including cold weather [13] and, to a limited extent, menstrual periods [22]. In our study, the frequency of painful episodes was higher during a winter as compared to the rest of the year. A significant difference was observed between winter and summer ($P = 0.0078$) under the signed rank test in a relatively small sample. These results would favor the concept that cold weather may be a precipitating factor in painful episode development, and would differ from earlier studies [13]. The difference between the studies may be related to the more precise daily recordings and the longer-term evaluation of episode occurrence in the present study.

Menses may be a contributory factor to painful episodes in some patients. Examination of the association between frequency of painful episodes and menses and menses and painful episodes showed a moderately close relationship (42% and 69%, on average, respectively). The average relative risk of ''sickle pain'' itself occurring during menses was not significantly increased as compared to the relative risk of sickle pain occurring during nonmenstrual time (1.6:1); however, 2 patients did have high relative risks of having sickle pain during menses (patient 1, 2.41:1; patient 8, 2.43:1; see Table III). No association between the shorter-lasting episodes and the occurrence of menses was observed.

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